Pressure-derived indices of left ventricular isovolumic relaxation in patients with hypertrophic cardiomyopathy

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SUMMARY   High fidelity measurements of left ventricular pressure were made at increasing pacing rates in 21 patients with hypertrophic cardiomyopathy and a control group of 11 patients investigated for chest pain who proved to have normal hearts. In both groups the fall in pressure during isovolumic relaxation from the point of min dp/dt approximated closely to a monoexponential, and could be described by a time constant and asymptote.

The time constant shortened and the asymptote increased as heart rate rose in both groups. The time constant was longer and min dp/dt less in the cardiomyopathy group than controls at all heart rates. In the cardiomyopathy patients min dp/dt, but not the time constant, was related to systolic pressure. During pacing, eight cardiomyopathy patients developed metabolic evidence of myocardial ischaemia, but indices of relaxation did not differ between these eight and the other 13 either at basal heart rate or the highest pacing rate.

In 10 cardiomyopathy patients measurements were repeated at comparable pacing rates after propranolol (0·2 mg/kg). Left ventricular end-diastolic pressure and indices of contractility decreased after the drug, but the time constant did not change. Eight patients received verapamil (20 mg) after which there were substantial reductions in systolic pressure and contractility. Min dp/dt decreased in proportion to systolic pressure, but the time constant was unchanged. At the highest pacing rate before drug administration three patients had abnormal lactate extraction which was corrected by either propranolol (one patient) or verapamil (two patients). Despite abolition of metabolic evidence of ischaemia, relaxation did not improve.

It is concluded that abnormal isovolumic relaxation is common in patients with hypertrophic cardiomyopathy, but its severity correlates poorly with other features of the disease. Abnormal relaxation is not the result of ischaemia, and pressure derived indices of relaxation do not improve after the administration of propranolol or verapamil.

Impairment of left ventricular relaxation and diastolic function is common in patients with hypertrophic cardiomyopathy[1-5] and may reflect the severity and distribution of inappropriate hypertrophy [3 4] or be the result of myocardial ischaemia.[1 5] Relaxation and diastolic function can improve after the administration of beta blocking drugs[1 6] or verapamil.[5] It is uncertain whether these drugs act directly upon the diseased myocardium[5] or by relieving ischaemia.[1]

The physiology of ventricular relaxation is poorly understood[7] and its study is limited by the lack of

methods of quantifying isovolumic pressure fall. Min dp/dt is measured easily, but describes only one point during relaxation, and because it depends upon systolic pressure[8] is of little use in comparing patients or investigating drugs that change arterial pressure. The fall in left ventricular pressure from the point of min dp/dt until mitral valve opening approximates to a monoexponential so that the rate of relaxation can be described by a time constant[9-11] which, in contrast to min dp/dt, characterises pressure fall throughout the majority of isovolumic relaxation, and is insensitive to systolic pressure.[9] Unfortunately the usual method of estimating the time constant, from the slope of ln

(pressure) against time,[9-11] has serious deficiencies which have been discussed in detail elsewhere.[12-14] An alternative method of exponential analysis has been developed and the model upon which it is based and the accuracy of its estimates of the time constant and asymptote of isovolumic pressure fall have been validated in patients with a variety of left ventricular disease.[13 14] In patients with coronary artery disease the time constant so derived is sensitive to myocardial ischaemia.[13]

We have applied this method to measurements of left ventricular pressure made in 21 patients with hypertrophic cardiomyopathy and a control group of 11 patients who proved to have normal hearts. Our purpose was to measure the severity of impaired relaxation in hypertrophic cardiomyopathy, investigate its relation to ischaemia, and to determine whether propranolol or verapamil could improve relaxation.

Patients and methods

Twenty one patients with hypertrophic cardiomyopathy were studied during diagnostic cardiac catheterisation. The control group consisted of 11 patients investigated for chest pain who proved to have normal hearts. Details of some of the patients in both groups have been reported previously.[14 15]

CARDIAC CATHETERISATION
The procedure was approved by the hospital's ethical committee. The catheter procedure has been described in detail elsewhere.[15 16] Briefly, diagnostic catheterisation was performed via the right femoral vein and artery. In the cardiomyopathy patients the gradient was derived from simultaneous measurements of left ventricular body and outflow pressures. Where appropriate, amyl nitrate or an extrasystole was used to provoke a gradient. The left heart catheter was replaced by a micromanometer (either Telco MM52, Gaeltec No. 8, or Millar No. 5) via a long sheath.[17] A Ganz catheter was positioned in the coronary sinus via a left arm vein. Left ventricular pressure was measured and coronary sinus and left ventricular blood sampled at basal heart rate and during incremental coronary sinus pacing. Measurements and samples were repeated at comparable pacing rates in 10 cardiomyopathy patients 20 minutes after propranolol (0·2 mg/kg iv), and in eight cardiomyopathy patients seven minutes after verapamil (20 mg). Ventricular cineangiography was performed at the end of the study.

MEASUREMENT OF LEFT VENTRICULAR PRESSURE
The sternal angle was used as zero reference. Left ventricular pressure was measured simultaneously by the catheter tip micromanometer and the lumen of the catheter, or via the long sheath when a 5 Millar was used. The catheter laboratory computer digitised the micromanometer signal at 5 ms intervals and the lumen pressure every 10 ms. As previously described, the lumen pressure was used to calibrate the micromanometer for the analysis of each pressure record.[13 14]

ESTIMATION OF TIME CONSTANT
In each beat the computer recognised the period of isovolumic relaxation to be analysed as starting at the time of min dp/dt and ending when pressure decreased to the level of end-diastolic pressure of the preceding beat.[9 11 13 14] The analysis was based upon a monoexponential of which the time constant and asymptote are variable.[13 14] Thus $P(t) = ae^{bt} + c$ where $P(t)$ = pressure at time t, t = time in ms after min dp/dt, and c = the asymptote. The time constant $= -\frac{1}{b}$. In each beat, by analysing successive sets of three points on the digitised pressure-time curve, the computer calculated the time constant and asymptote. This method of analysis has been described in detail elsewhere.[14]

The computer also calculated systolic and end-diastolic pressures, max dp/dt, min dp/dt, and KVmax (from developed pressure[18]) for each beat. The values that appear in the results are the mean of all the beats in a nine second record.

LACTATE CONCENTRATION
Blood samples were added to an aliquot of perchloric acid, frozen, and subsequently analysed by a photofluorometric method.[19] Extraction ratio is the difference between lactate concentrations in left ventricular and coronary sinus blood expressed as a percentage of its concentration in left ventricular blood ($^{a-v}/A\%$).

STATISTICAL METHODS
To test the validity of the exponential model the pressures predicted by the estimates of the time constant and asymptote were compared with measured pressure in 44 beats. The "goodness of fit" was assessed by the ratio of the residual to total sum of squares (RSS/TSS).

Elsewhere Student's t test and linear regression were used. Values are expressed at mean ± SEM. $p < 0.05$ is considered significant.

Results

The details of the patients with hypertrophic cardiomyopathy are listed in Table 1. Each had clinical, electrocardiographic, and angiographic evidence of left ventricular hypertrophy. Sixteen patients had

Table 1   *Details of patients with hypertrophic cardiomyopathy*

Case No.	Age (y)	Sex	Resting gradient (mmHg)	Basal lactate (%)	Lactate extraction ratio at highest pacing rate (%)
1	23	F	61	44	3
2	43	F	36	59	−16
3	53	F	100	25	−11
4	42	M	49	36	45
5	39	M	5	20	19
6	58	M	26	38	25
7	24	M	70	56	30
8	41	M	27	57	29
9	26	M	22	35	21
10	29	F	69	38	3
11	47	M	41	36	18
12	33	M	14	36	21
13	49	M	9	15	29
14	60	F	3†	39	34
15	18	F	27	26	−19
16	28	M	0‡	17	−33
17	22	F	0*	18	3
18	17	M	0*	35	18
19	28	F	0*	36	11
20	57	M	0*	8	−15
21	46	M	0*	55	44

*Gradient not provoked by amyl nitrate or postextrasystole.
†Gradient 53 during amyl nitrate inhalation.
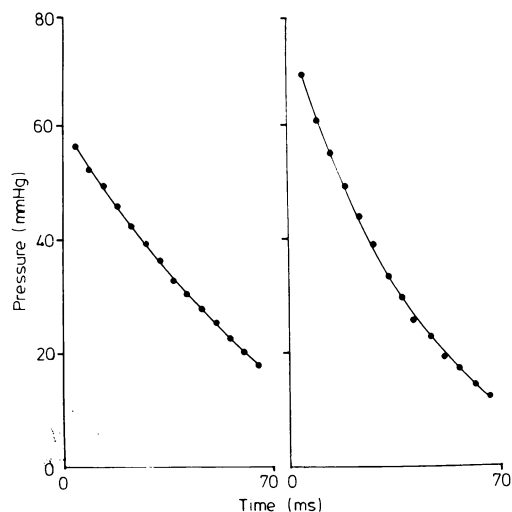‡Gradient 15 during amyl nitrate inhalation.

Fig. 1   *Comparison of measured pressure with pressures predicted by the estimates of the time constant and asymptote.* ● *measured pressure digitised at 5 ms intervals. Solid line: pressures predicted by exponential model. Left hand panel: a beat recorded at basal heart rate in a patient with hypertrophic cardiomyopathy. The time constant = 129 ms and the asymptote −41 mmHg. When measured and predicted pressures are compared RSS/TSS = 0·2%. Right hand panel: a beat recorded at basal heart rate in one of the controls. The time constant = 55 ms, and the asymptote −14 mmHg. RSS/TSS = 0·2%.*

outflow obstruction either at rest (15) or after amyl nitrate inhalation (one). In five patients a gradient could not be provoked by amyl nitrate or an extrasystole. Nineteen of the 21 had normal selective coronary arteriograms; one patient (case 13) had minor disease, and in the remaining patient normal proximal coronary arteries were demonstrated by aortography (case 15).

The 11 control subjects each had normal coronary arteriograms and did not develop pain or electrocardiographic abnormalities during pacing. Lactate concentrations were measured in nine. Myocardial lactate production was not observed and the lactate extraction ratio did not change significantly between basal heart rate and the highest pacing rate (28% ± 4 to 23% ± 4).

The pressures predicted by the estimate of the time constant and asymptote were compared with measured pressure in 32 beats recorded in eight patients with cardiomyopathy, and 12 beats from six normal subjects. Two examples are illustrated in Fig. 1. The beats analysed included examples at different pacing rates, and in the cardiomyopathy group beats recorded before and after drug administration. For beats from the cardiomyopathy group RSS/TSS ranged from 0·1% to 1·9%; in 25 it was less than 0·5%, and in five between 0·5% and 1%. For the controls RSS/TSS ranged from 0·1% to 0·8%; in six it was less than 0·5%.

Table 2 lists the haemodynamics in both groups at basal heart rate and the highest pacing rate. Min dp/dt was lower and the time constant longer in the car-

Table 2 *Comparison of hypertrophic cardiomyopathy group with controls: values expressed as mean ± SEM*

	Heart rate (bpm)	LVSP (mmHg)	LVEDP (mmHg)	KVmax/s	Max dp/dt (mmHg/s)	Min dp/dt (mmHg/s)	T (ms)	Asymptote (mmHg)
Basal heart rate								
HCM (n = 21)	82 ± 3	118 ± 6	12 ± 1	85 ± 4	1260 ± 92	−1078 ± 66	77 ± 6	−27 ± 4
Controls (n = 11)	90 ± 6	121 ± 5	6 ± 2 p < 0·001	93 ± 4	1594 ± 65 p < 0·005	−1863 ± 75 p < 0·001	52 ± 4 p < 0·001	−22 ± 3
Highest pacing rate								
HCM (n = 21)	137 ± 4	104 ± 4	12 ± 2	90 ± 6	1350 ± 85	−934 ± 71	57 ± 5	−10 ± 3
Controls (n = 11)	147 ± 7	118 ± 6	1 ± 1 p < 0·001	106 ± 6	2096 ± 91 p < 0·001	−2025 ± 100 p < 0·001	32 ± 2 p < 0·001	−8 ± 2

LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; Max dp/dt, maximum rate of rise of LV pressure; Min dp/dt, minimum rate of fall of LV pressure; T, time constant of LV pressure fall.

Table 3 *Comparison of patients with and without obstruction*

	Heart rate (bpm)	LVSP (mmHg)	LVEDP (mmHg)	KVmax/s	Max dp/dt (mmHg/s)	Min dp/dt (mmHg/s)	T (ms)	Asymptote (mmHg)	LER (%)
Basal heart rate									
Obstructive (n = 16)	83 ± 4	126 ± 7	11 ± 1	86 ± 4	1344 ± 67	−1179 ± 66	67 ± 4	−28 ± 4	36 ± 3
Non-obstructive (n = 5)	79 ± 5	95 ± 4 p < 0·05	13 ± 1	82 ± 5	990 ± 98 p < 0·02	−759 ± 84 p < 0·01	114 ± 13 p < 0·01	−26 ± 6	30 ± 8
Highest pacing rate									
Obstructive (n = 16)	140 ± 4	106 ± 4	11 ± 2	90 ± 8	1412 ± 98	−1048 ± 82	53 ± 5	−10 ± 3	12 ± 6
Non-obstructive (n = 5)	131 ± 8	97 ± 3	13 ± 5	89 ± 4	1157 ± 124	−812 ± 97	67 ± 11	−9 ± 4	12 ± 10

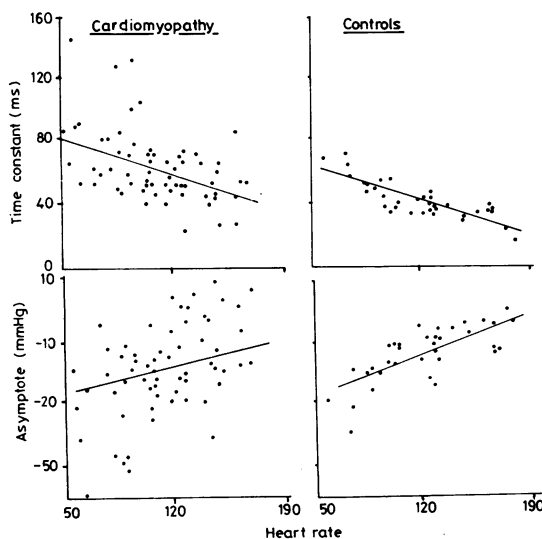LER, lactate extraction ratio. Other abbreviations as in Table 2.

Fig. 2 *Upper panels: the individual values of the time constant have been plotted against heart rate in the 21 patients with cardiomyopathy (left) and the 11 controls (right). In both groups the time constant shortened as heart rate increased: for the cardiomyopathy group r = −0·42, p < 0·001, and for the controls r = −0·83, p < 0·001. Lower panels: individual values of the asymptote in the cardiomyopathy patients (left) and controls (right) plotted against heart rate. For the cardiomyopathy patients r = 0·25, p < 0·05, and for the control group r = 0·70, p < 0·01.*
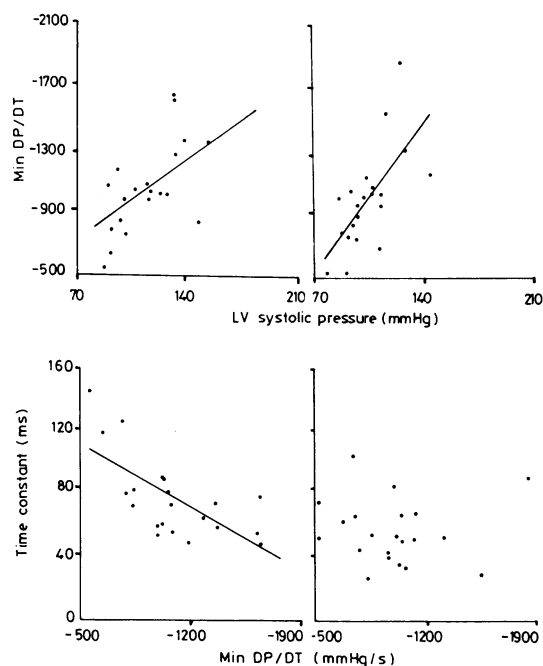
Fig. 3 *Upper panels. The relation between min dp/dt and left ventricular systolic pressure in the 21 cardiomyopathy patients at basal heart rate (left) and the highest pacing rate (right). At basal heart rate r = 0·68, p < 0·01, and at the highest pacing rate r = 0·67, p < 0·01. Lower panels: the time constant has been plotted against min dp/dt in the 21 cardiomyopathy patients at basal heart rate (left) and the highest pacing rate (right). At basal heart rate r = −0·67, p < 0·01. The significance of the correlation is largely the result of the three patients who have the worst values of both indices of relaxation. At the highest heart rate the time constant and min dp/dt were not related significantly.*

diomyopathy group compared with controls at both heart rates. In both groups the time constant shortened and the asymptote increased between basal heart rate and the highest pacing rate. When all heart rates were considered the time constant was related inversely and the asymptote positively to heart rate

(Fig. 2) in both groups. Min dp/dt increased with heart rate only in the controls. End-diastolic pressure was greater and max dp/dt lower in the cardiomyopathy patients compared with controls at both basal heart rate and the highest pacing rate. KVmax and max dp/dt increased, and end-diastolic pressure decreased with pacing in the controls but not in the cardiomyopathy group.

In the cardiomyopathy patients there was wide variation in the indices of relaxation. Only at basal heart rate was there correlation between min dp/dt and the time constant (Fig. 3). Min dp/dt was related to systolic pressure at both heart rates (Fig. 3), but the time constant was not related to pressure, or to indices of contractility. At basal heart rate the time constant was longer and min dp/dt lower in the patients without obstruction (Table 3), but in the patients with obstruction the time constant could not be related to the gradient.

In the cardiomyopathy patients at basal heart rate myocardial lactate extraction ratio was 35% ± 3, and was greater than 10% in all but one (Table 1). At the highest pacing rate extraction ratio decreased to 12% ± 5. This reduction was largely because of eight patients who produced lactate or had extraction ratio of <5% during pacing (Table 1). The haemodynamics of these eight and the other 13 are compared in Table 4. No differences were found between these two subgroups. In particular the indices of relaxation were comparable.

Measurements were repeated after propranolol in 10 cardiomyopathy patients (Table 5). At the lowest heart rate max dp/dt decreased after the drug, but the indices of relaxation did not change. At the highest pacing rate after the drug there were significant reductions in systolic and end-diastolic pressure, max dp/dt, KVmax, and min dp/dt, but the time constant was unchanged. Before the drug four of the 10 patients developed low or negative lactate extraction ratios during pacing. After the drug, extraction ratio improved substantially in only one patient, from 2·7% to 44%. This was not accompanied by major improvement in relaxation; min dp/dt decreased from

Table 4 *Comparison of patients with normal and abnormal lactate extraction*

	Heart rate (bpm)	LVSP (mmHg)	LVEDP (mmHg)	KVmax/s	Max dp/dt (mmHg/s)	Min dp/dt (mmHg/s)	T (ms)	Asymptote (mmHg)	LER (%)
Basal heart rate									
Normal (n = 13)	81 ± 4	119 ± 6	11 ± 1	83 ± 4	1235 ± 69	−1062 ± 79	79 ± 8	−28 ± 5	36 ± 3
Abnormal (n = 8)	85 ± 6	118 ± 6	13 ± 3	88 ± 7	1308 ± 145	−1107 ± 141	75 ± 9	−26 ± 7	30 ± 8
Highest pacing rate									
Normal	132 ± 4	107 ± 5	12 ± 3	89 ± 5	1394 ± 128	−1013 ± 110	57 ± 6	−10 ± 4	26 ± 3
Abnormal	147 ± 6	97 ± 4	11 ± 2	91 ± 15	1286 ± 67	−958 ± 49	58 ± 7	−10 ± 3	−11 ± 5 p < 0·00

Abbreviations as in Tables 2 and 3.

Table 5 *Effects of propranolol*

	Heart rate (bpm)	LVSP (mmHg)	LVEDP (mmHg)	KVmax/s	Max dp/dt (mmHg/s)	Min dp/dt (mmHg/s)	T (ms)	Asymptote (mmHg)
Lowest pacing rate								
Before propranolol (n = 10)	86 ± 5	126 ± 11	11 ± 1	87 ± 6	1437 ± 86	−1206 ± 83	69 ± 6	−32 ± 5
After propranolol (n = 10)	89 ± 5	119 ± 9	8 ± 2	78 ± 6	1160 ± 148 $p < 0.05$	−1139 ± 89	62 ± 3	−22 ± 5
Highest pacing rate								
Before propranolol (n = 10)	132 ± 7	121 ± 9	13 ± 1	101 ± 7	1540 ± 99	−1160 ± 87	54 ± 5	−15 ± 4
After propranolol (n = 10)	132 ± 7	106 ± 6 $p < 0.02$	8 ± 1 $p < 0.01$	82 ± 6 $p < 0.05$	1301 ± 72 $p < 0.01$	−1009 ± 73 $p < 0.02$	55 ± 4	−14 ± 5

Abbreviations as in Table 2.

Table 6 *Effects of verapamil*

	Heart rate (bpm)	LVSP (mmHg)	LVEDP (mmHg)	KVmax/s	Max dp/dt (mmHg/s)	Min dp/dt (mmHg/s)	T (ms)	Asymptote (mmHg)
Lowest pacing rate								
Before verapamil (n = 8)	86 ± 7	115 ± 10	12 ± 2	82 ± 4	1104 ± 48	−905 ± 87	90 ± 13	−26 ± 5
After verapamil (n = 8)	85 ± 7	95 ± 6 $p < 0.01$	10 ± 3	69 ± 5 $p < 0.05$	902 ± 60 $p < 0.005$	−767 ± 64 $p < 0.005$	93 ± 12	−24 ± 4
Highest pacing rate								
Before verapamil (n = 7)	119 ± 7	114 ± 9	10 ± 2	82 ± 4	1262 ± 117	−957 ± 101	65 ± 4	−16 ± 6
After verapamil (n = 7)	113 ± 7	96 ± 6 $p < 0.01$	7 ± 2	70 ± 2 $p < 0.02$	943 ± 55 $p < 0.01$	−795 ± 70 $p < 0.01$	65 ± 7	−12 ± 3

Abbreviations as in Table 2.

−1448 to −1037 mmHg/s, and the time constant from 65 to 58 ms.

Measurements were repeated after verapamil in eight cardiomyopathy patients at the lowest heart rate and in seven at the highest pacing rate (Table 6). After the drug at both heart rates there were significant reductions in systolic pressure, KVmax, max dp/dt, and min dp/dt, but no change in the time constant. Before verapamil two patients had low or negative lactate extraction ratios at the highest pacing rate (3% and −15%) which increased after the drug (38% and 11%). Despite increased lactate extraction, indices of relaxation did not improve after the drug: min dp/dt decreased from −560 to −501 mmHg/s and from −1046 to −837 mmHg/s, but the time constant was unchanged; 61 and 59 ms, and 60 and 59 ms.

Discussion
Our method of estimating the time constant, and the model upon which it is based, have been validated in patients with a variety of left ventricular disease.[13] [14] In the 44 beats tested in this study the pressures predicted by the estimates of the time constant and asymptote were in close agreement with measured pressure. It is legitimate, therefore, to describe isovolumic relaxation by a time constant estimated in this way.

Although left ventricular pressure fall during isovolumic relaxation approximates to a monoexponential in a wide range of circumstances,[14] relaxation of isolated muscle is not characterised by exponential tension decay[7] [20] even when the relaxation sequence of the intact ventricle is imitated.[7] [21] This difference between isolated muscle and the left ventricle might be the result of the difficulty of simulating the complex load system of the heart, ventricular geometry, internal and external restoring forces operating upon the ventricular myocardium,[22] [23] regional variation in the time of onset of relaxation, or the effect of coronary perfusion pressure.[24] Clearly the time constant of pressure fall describes the overall behaviour of a complicated system, and though relaxation of the ventricle and isolated muscle must have a common mechanism it is unlikely that the time constant measures the rate of a specific process occurring in the ventricle's constituent muscle fibres.

The exponential course of pressure fall can be interpreted in two ways. Once relaxation has started pressure and its rate of change are time dependent. Alternatively, the time constant describes the instantaneous relation between pressure and its rate of change. In the Appendix it is shown that for an exponential model dp/dt is related linearly to pressure; the slope is the negative reciprocal of the time constant,

and the intercept on the pressure axis is the asymptote. In this sense the rate of relaxation at any time after min dp/dt is "load-dependent", though this may not be strictly analogous to the load dependent component of relaxation in isolated muscle.[7 20] At a given pressure, at any time after min dp/dt, when the time constant is long the rate of pressure fall is less than when the time constant is short. It is also shown in the Appendix that min dp/dt is determined by pressure, the time constant, and the asymptote.This is consistent with the known pressure dependence of min dp/dt[8] and the poor correlation between min dp/dt and the time constant found in our cardiomyopathy patients in whom systolic pressure varied widely between individuals.

At basal heart rate and during pacing the time constant was longer and min dp/dt lower in the cardiomyopathy patients compared with controls, whereas the asymptote was comparable in the two groups. As heart rate increased the time constant became shorter and the asymptote rose towards zero in both groups. Within the cardiomyopathy group there was wide individual variation in the indices of relaxation. As might be expected, min dp/dt correlated with systolic pressure, but the time constant could not be related to systolic pressure, the gradient, or indices of contractility.

At basal heart rate myocardial lactate extraction ratio was similar in the two groups, and only one of the cardiomyopathy patients had an extraction ratio less than 10%. It is unlikely, therefore, that prolongation of the time constant at basal heart rate in the cardiomyopathy patients was the result of ischaemia. During pacing lactate extraction ratios remained high in 13 of the cardiomyopathy patients, but in eight the ratios decreased to low or negative values. Indices of relaxation did not differ between these two subgroups either at basal heart rate or at the highest pacing rate. Thus, there was no evidence that ischaemia was the major cause of abnormal relaxation, or that impaired relaxation predisposes to ischaemia during pacing.

It could be argued that in the eight patients with abnormal lactate extraction the severity of ischaemia was insufficient to affect relaxation. Their lactate extraction ratios, however, were comparable to those measured in this laboratory in patients with coronary artery disease during pacing-induced angina[16 25] in whom prolongation of the time constant is a sensitive index of ischaemia.[13] In addition, four of these eight patients experienced chest pain during pacing. The apparent lack of effect of ischaemia suggests that the reduced rate of relaxation is the result of the primary myocardial abnormality and that ischaemia has little additional effect. Alternatively, the consequences of ischaemia might depend upon its site. Because of abnormal fibre orientation[26] and the shape of the sep-

tum[27] the tension generated by some parts of the myocardium makes little contribution to ventricular cavity pressure. By the same argument prolongation of tension decay in ischaemic septal fibres would have little effect upon the time course of intracavity pressure fall in patients with hypertrophic cardiomyopathy.

Beta blocking drugs are known to improve left ventricular diastolic distensibility and reduce end-diastolic pressure in patients with hypertrophic cardiomyopathy.[1 15] In this study propranolol, administered at a dose sufficient to reduce contractility and end-diastolic pressure, did not change the time constant. Therefore propranolol did not have a direct effect upon isovolumic relaxation, and it is unlikely that its beneficial action upon diastolic function is caused by acceleration of relaxation.

Acutely, verapamil reduces the duration of isovolumic relaxation and increases the maximum rate of early diastolic filling in patients with hypertrophic cardiomyopathy.[5] In this study we administered a large dose which caused substantial reductions in systolic pressure and indices of contractility. Min dp/dt decreased in proportion to systolic pressure after the drug, but the time constant and asymptote did not change. Judged by our pressure derived indices isovolumic relaxation is not influenced favourably by verapamil.

Of the 10 patients given propranolol, four had metabolic evidence of ischaemia at the highest pacing rate before the drug. In one of these four lactate extraction increased substantially after the drug, but indices of relaxation did not change. Similarly, verapamil administration increased lactate extraction in two patients at the highest pacing rate, but failed to reduce the time constant. Thus even when they abolish metabolic evidence of myocardial ischaemia neither propranolol nor verapamil increases the rate of isovolumic pressure fall.

From this study it is concluded that both in normal subjects and patients with hypertrophic cardiomyopathy the rate of isovolumic relaxation can be described by a time constant. In most patients with hypertrophic cardiomyopathy the time constant is prolonged, but the severity of abnormal relaxation correlates poorly with other features of the disease. Ischaemia is not the major cause of impaired relaxation. Neither propranolol nor verapamil improves isovolumic relaxation, even when they abolish metabolic evidence of myocardial ischaemia.

Appendix

The exponential model of pressure fall is

$$P(t) = ae^{bt} + c \qquad (1)$$

where P(t) = pressure at time t

   (t) = time after min dp/dt

   (c) = the asymptote

   (a) = P(o) − c (where P(o) = pressure at the time of min dp/dt)

the time constant, $T = -\dfrac{1}{b}$

by differentiation equation (1) becomes

$$^{dp/dt}(t) = ae^{bt}.b \qquad (2)$$

by substitution in equation (1)

$$P(t) - c = ae^{bt} \qquad (3)$$

Dividing (2) by (3)

$$\frac{dp/dt}{P(t) - c}(t) = b$$

Thus the rate of change of pressure is related to pressure by the slope b (of which the time constant is the negative reciprocal)

When P(t) = c dp/dt(t) = 0 .

Thus the asymptote is the intercept on the pressure axis.

By definition min dp/dt occurs at time 0.

From equation (2)

min dp/dt = a.b.

and by substitution

$$\text{min dp/dt} = \frac{P_{(o)} - c}{-T}$$

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